

**Should a reduction in all-cause mortality be the goal when assessing preventive medical therapies?**

**Short title:** All-cause mortality should not always be studied

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Traditionally, innovations in cardiovascular medicine (including preventive therapies) have been assessed in terms of cause-specific morbidity and mortality. More recently, some have argued that such therapies should not be used unless they have been shown to reduce all-cause mortality. Here we argue that such an approach is bad science and makes a mockery of evidence-based medicine.

Cardiovascular therapeutics should aim to reduce mortality, but it is not necessary to demonstrate a reduction in all-cause mortality when assessing them. It is, in general, misguided to attempt to demonstrate such an effect, because it is too crude a measure of either benefit or harm. Results are dominated by causes of death unrelated to the intervention – the signal to noise ratio is very low. Most effective interventions in public health and preventive medicine that have, together, led to substantial improvements in life-expectancy would not have been introduced, had policy makers required direct evidence of an impact on all-cause mortality.

An example of misinterpretation of the data is the systematic review by the US Preventive Services Task Force<sup>1</sup> of screening for AAA, “One-time invitation for abdominal aortic aneurysm (AAA) screening in men aged 65 years or older was associated with decreased AAA rupture and AAA-related mortality rates but had little or no effect on all-cause mortality rates”. This summary ignores the compelling evidence in favour of AAA screening being of overall benefit: the hazard ratio (HR) for deaths from aortic aneurysms was 0.60 ( $P=10^{-12}$ ), and there was no evidence of an increase in deaths from other causes. Together this is sufficient to make the case for screening.

Even relying on a meta-analysis of randomized controlled trials with a non-significant result for all-cause mortality to argue that an intervention is useless is scientifically wrong, and unethical, when there is clear disease-specific benefit and no evidence of hazard.

From the perspective of the trial design of preventive interventions, the endpoint of all-cause mortality is neither sensitive nor specific. Suppose a particular cause (X) is responsible for 5% of all deaths in the target population over the next 15 years, and consider an intervention that prevents 70% of deaths from X (see [a] in Figure). Suppose 3% of the target population will die over the next 15 years. If all-cause mortality were the end-point it would need 1,095,000 individuals randomized equally between the intervention and no intervention to have 90% power to show the benefit; but using cause-specific mortality it would need only 41,000 individuals. How is it possible to justify conducting a study that is over 25 times larger than needed? Conversely, using all-cause mortality to guide decisions regarding futility in clinical trials may be misguided as shown in example [b] (Figure).

Specifying the primary end-point to be cause-specific mortality rather than all-cause mortality does not mean that serious adverse events due to an intervention are ignored. These are recorded, and if

there is a significant excess of a particular cause of death, that is taken into account when considering the overall balance of harms and benefits of the intervention. An example is offered from the early studies of radiotherapy in the treatment of breast cancer. There was a significant reduction in loco-regional recurrence, but also a significant excess of cardiac deaths and no overall benefit<sup>2</sup>. Subsequent improvements in radiotherapy resulted in far less radiation exposure in the heart and major blood vessels, and this shifted the harm-benefit ratio so that effect on breast-cancer mortality was maintained and the effect on cardiac mortality almost eliminated. Had the focus of assessing radiotherapy been all-cause mortality alone, an important treatment with substantial benefit in overall survival might never have been introduced, as initially there was no overall benefit.

Another problem with using all-cause mortality is that the impact of an intervention on all deaths will depend on the underlying risk of those diseases that it affects and is likely to be different in different populations. Many interventions have a relative impact on a disease that is similar to and independent of the underlying risk of the disease. Suppose, for instance, an intervention reduces the risk of dying from A by 30% (HR =0.7) but increases the risk from B by 100% (HR=2.0) (see [c] in Figure). Then, if death from A is three to four times as common as B, the benefits and harms are finely balanced (Population 1), but in a population where A is forty times more common than B (Population 2) the benefits greatly exceed the harms in terms of all-cause mortality. Comparison of coronary artery bypass grafting (CABG) with medical therapy in patients with heart failure provides a good example<sup>3</sup>. The randomized controlled trial found that CABG has a consistent beneficial effect on cardiovascular mortality regardless of age and no effect on non-cardiovascular mortality, but somewhat surprisingly emphasized that CABG has a more substantial benefit on all-cause mortality in younger compared with older patients.

The Cholesterol Treatment Trialists (CTT) Collaboration of statin therapy illustrates the insensitivity of all-cause mortality when trying to identify signals of benefit in the prevention of major vascular events (see [d] in Figure)<sup>4</sup>. All-cause mortality ignores the benefits of prevention on non-fatal events, and mixes vascular deaths (which statins prevent) with non-vascular deaths (which they don't). All-cause mortality is not generalizable to groups of patients with different proportions of vascular and non-vascular deaths.

Evidence-based medicine should not be about withholding interventions until they have been proven to reduce overall mortality. It should be analytical and intelligent – assessing the efficacy and harms of an intervention separately, and then applying these estimates to populations that might be offered the intervention, taking all evidence into account, including an assessment of whether it provides reasonable value for money.

Figure. Examples of the inappropriate use of all-cause mortality: [a] Huge numbers of patients are required to show efficacy in terms of all-cause mortality even when there is a highly significant effect on cause-specific mortality; [b] Conversely, use of all-cause mortality would require continuation of a trial that was, based on cause-specific mortality, clearly futile; [c] If therapy prevents one disease but increases the risk of another, its impact on all-cause mortality made be very different in different populations; [d] Cholesterol prevents major vascular events to the same (relative) extent in all groups, but its impact on all-cause mortality increases with the underlying risk of vascular disease.

#### Conflict of Interest Disclosures

PS: None

NW: None

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